Remarks/Arguments

I. Status of the Claims:

Claims 141,150.155-160 and 162-173 stand rejected. Claim 160 is cancelled without prejudice or disclaimer. No claims are added. Claims 141, 150, 155, 156, 166 and 169 are presently amended. Claims 141, 150, 155-159 and 161-173 are pending in the case.

II. Claim Objections:

Claims 150, 155 – 160 and 162 – 163 are objected to for allegedly failing to further limit the scope of claim 141 from which they depend (see Office Action, page 2, Section 2). Specifically, the Examiner contends that the transitional phrase of claim 141 was previous amended to "consists of" and that "[c]laims 150, 155-160 and 162-163 seek to introduce new elements and in numerous cases uses the expression 'comprises', which opens up the claims to include a limitless number of additional, unidentified components" (see, e.g., page 2, section 2, lines 6-8). Applicant disagrees in part with these objections.

With respect to claims 150, 155, and 156, the transitional phrase "comprising" has been removed, and the claims have been amended to recite "wherein at least 3 of the plurality of double stranded nucleic acid fragments have a size greater than 1 kb, and wherein at least 3 of the double stranded nucleic acid fragments have a size less than 1 kb", in combination with the features set forth in claim 141. Applicant believes this amendment clarifies claims 150, 166 and 156, and respectfully requests that the objections thereto be withdrawn. Additionally, claim 160 has been canceled without prejudice or disclaimer.

With respect to claims 157 – 159, 162 and 163, Applicant respectfully disagrees with these objections. Claim 157 recites the feature "wherein the plurality of double stranded nucleic acid fragments are stained with a detectable label" in combination with the features set forth in claim 141. Contrary to the Examiner's assertions, the language of claim 157 does not broaden the scope of the claim (i.e., does not recite additional elements above and beyond "the plurality of double stranded nucleic acid fragments") set forth in claim 141. Instead, claim 141 recites additional limitations on the plurality of double stranded nucleic acid fragments already recited. In this regard, MPEP §2111.03 states "[a] claim which depends from a claim which "consists of" the recited elements or steps cannot add an element or step". Similarly, claims 158 and 159 do not add any additional steps or elements beyond the plurality of double stranded nucleic acid fragments already recited in claims 141 and 157, but merely place additional limitations on

the types of dyes that can be used in claim 157. Accordingly, for at least these reasons, Applicant respectfully requests that the objections to claims 157-159 be removed.

Claims 162 and 163 recite the features "wherein the relative mass of any one fragment of the plurality is no more than 2.5 (2) times the relative mass of any other fragment of the plurality", respectively. Similar to the arguments made above with respect to claim 15-159, claim 162 and 163 in fact do not recite any additional elements or steps beyond the plurality of double stranded nucleic acid fragments already recited in claim 141, but instead place further limitations on the characteristics of the plurality of double stranded nucleic acid fragments. Accordingly, for at least these reasons, Applicant respectfully requests that the objections to claims 162 and 163 be removed.

III. Rejections Under 35 U.S.C. § 112:

Claims 141, 150, 155-160, 162-164 and 166-168 stand rejected under the definiteness requirement of 35 U.S.C. §112. The Examiner contends that "said claim 41, however still retains multiple usage of the term 'comprising' to define the possible fragments. The presence of both consisting and comprising in the same sentence leaves the metes and bounds of the claim in doubt" (Office action, page 3, section 5). Without agreeing with or acquiescing to the rejections, and solely to expedite prosecution of the case and allow its passage to issue, Applicant has amended the language of claim 141 to recite, in part "wherein at least two of the plurality of nucleic acid fragments have a size greater than 1 kb, and wherein at least two of the plurality of nucleic acid fragments have a size less than 1 kb". Additionally, Applicant has amended the transitional phrase of the claim 141 from "consisting of" to "consisting essentially of" (see below for further discussion of same.

With regard to the Examiner's statements regarding claims 156 and 157, Applicant respectfully refers to the statements made above in section II of this paper relating to same. Namely, the dependent claims do not add additional elements not already present in claim 141, but rather impose further limitations on the existing claim elements.

With regard to claim 141, the Examiner states "(the claim) makes reference to the 'relative mass' of a fragment of nucleic acids and, in part, defines it in term of the copy number of a given fragment. This asserted relationship is confusing as a fragment has mass on its own. Having more of a given fragment does not alter the mass of the individual molecules. Seemingly, applicant is attempting to make reference to the mass of a band in a gel; however, the claimed invention is not part of a gel. Indeed, by applicant using the term 'consisting of,' the DNA fragments have been construed as being in a desiccated state" (Office

action, page 3). Applicant respectfully traverses this rejection. Claim 141 recites, in part, "each fragment having a size in base pairs of between 20 kb and 100 base pairs, a copy number, a mass, and a relative mass, wherein the mass of each fragment is the size in base pairs of the fragment multiplied by the copy number of the fragment, wherein the relative mass of each fragment is the mass of the fragment divided by the sum of the masses of all of the fragments, wherein the relative mass of any one fragment of the plurality is no more than 3 time the relative mass of any other fragment of the plurality". It appears that the Examiner has confused the term "relative mass" with the art recognized term "molecular mass", which is equivalent to the claimed term "size in base pairs". For clarification, Applicant respectfully points out that the claimed term "mass" refers not to the molecular weight of each individual fragment (i.e., the size of each fragment in base pairs), but rather to the amount of material (i.e., nucleic acid) present in each fragment. In this regard, the term "the mass of each fragment" is defined clearly and unambiguously in the claim as "the size in base pairs of the fragment multiplied by the copy number". Similarly, the term "relative mass", refers to the amount of material (i.e., nucleic acid) present in one fragment relative the amount of material present in all the fragments together. The term "relative mass" of a particular nucleic acid fragment is likewise clearly and unambiguously defined within the claim as "the mass of the fragment divided by the sum of the masses of all of the fragments". Additionally, the claim includes the further limitation that "the relative mass of any one fragment of the plurality is no more than 3 time the relative mass of any other fragment of the plurality". Therefore, Applicant respectfully submits that the Examiner's interpretation of the term "relative mass" as "[s]eemingly … attempting to make reference to the mass of a band in a gel" is erroneous, since the terms "mass", "relative mass" and "size in base pairs" are all clearly and unambiguously defined within the body of the claim and therefore would not cause the skilled practitioner any confusion. Accordingly, Applicant submits that one skilled in the art would readily understand the metes and bounds of the subject matter instantly claimed.

The Examiner also states "the DNA fragments have been construed as being in a desiccated state". Applicant disagrees with this interpretation of the claim, but has nevertheless amended the transitional phrase of claim 141 from "consisting of" to "consisting essentially of" solely for the purpose of clarification. Applicant believes this amendment does not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original), and sufficiently broadens the scope to include the presence of an aqueous solvent.

Claim 166 has been amended to correct the dependency.

Claims 169 stands rejected as allegedly being indefinite, since the Examiner is uncertain what constitutes a "highlighted fragment". While Applicant respectfully disagrees with this rejection and

submits that a person having ordinary skill in the art would readily understand what is meant by the phrase "highlighted fragment" in the context of the instantly claims nucleic ladders, claim 169 has nevertheless been amended solely in the interest of advancing prosecution of the case. Amended claim 169 recites, in part "wherein a copy number of the molecules is such that each molecule has a relative mass that is no more than three times the relative mass of another molecule and one or both of the following; i) wherein the nucleic acid ladder further comprises at least one additional molecule having a size in the range of 100 base pairs to 5 kilobase pairs and having a relative mass that is three times greater than the relative mass of other molecules in the composition, or; ii) wherein at least one of the three or more molecules has a relative mass that is three times greater than the relative mass of the other molecules in the composition".

In light of the arguments and the amendments made above, Applicant respectfully submits that claims 141, 150, 155-160, 162-164 and 166-168 are in compliance with the requirements set forth in 35 USC §112, second paragraph, and respectfully requests that the rejections thereof on these grounds be removed.

IV. Rejections Under 35 U.S.C. § 101:

Claims 150, 155 and 165-173 stand rejected under 35 USC §101, as allegedly being inoperative and therefore lacking utility for the reasons set forth sections 11-14 on pages 4 and 5 of the instant Office Action. For at least the reasons stated above in section III of this response, Applicant respectfully traverses these rejections. With regard to claims 150 and 155, the Examiner states "[c]learly, the 2 kb fragment would have a relative mass that is more than 3X the mass of the 400 by fragment … Accordingly, a composition comprising the fragments recited in claims 150 and 155 is not possible to achieve with respect to the factor of 3x mass limitation required in claim 141" (Office action, pages 4 and 5). With regard to claim 165, the Examiner states "[c]laim 165 requires that one select 3 or more fragments from one group and 3 or more fragments from a second group, and stipulates that the mass of more fragment cannot be more than 3x that of another fragment. The smallest fragment in the first group is 100 base pairs and thee smallest of the second group is 1 kb. Clearly, the mass of a 1 kb fragment is 10x that of the 100 by fragment" (Office action, page 5, section 13). Therefore, it appears that the basis for these rejections rests entirely on the apparently incorrect interpretations of the terms "size in base pairs", "mass" and "relative mass". However, as described above in section III of this response, the three terms are in fact distinct and not interchangeable. The claims define the **size** of a nucleic acid fragment as "size in base pairs" (i.e., the length of each

individual nucleic acid fragment). The "size in base pairs" is what determines how far a particular nucleic acid fragment will migrate in a gel during electrophoretic migration, which is **not** the same as the **mass** of the fragment. Indeed, the "size in base pairs" of a fragment is completely independent from the "mass" or of the "relative mass" of each nucleic acid fragment, as defined by the claims. Both the "mass" and the "relative mass" of each fragment do not refer to the size of each fragment, but rather are measures of the amount of material (i.e., nucleic acid material) present in each fragment on a weight basis. The claims define "mass" as "the size in base pairs of the fragment multiplied by the copy number of the fragment". While the mass of a fragment as defined in the claims is a function of its size, there is also an additional variable (namely copy number) that determines what the actual mass of nucleic acid in a fragment is. Thus, the mass of a fragment is determined not only by the size of that fragment, but also by the number of molecules (i.e., copy number) of that fragment present. Likewise, the term "relative mass" is defined in the claims as "the mass of the fragment divided by the sum of the masses of all of the fragments". Therefore, while both the mass and the relative mass of each fragment are functions of the size of the fragments, the copy number of each fragment may be manipulated to satisfy the other features of the claims, such as, e.g., "wherein the relative mass of any one fragment of the plurality is no more than 3 time the relative mass of any other fragment of the plurality". Therefore, Applicant submits that the Examiner's interpretation of the terms "size", "mass" and "relative mass", in the context of the instant claims is erroneous. As such, Applicant submits the claims are in fact operable and in accordance with the requirements of 35 USC §101 and requests that the rejections of claims 150, 155 and 165-173 under these grounds be removed.

Additionally, Applicant notes that in section 15-38, the Examiner takes the position that the claims are obvious over the Carlson reference (discussed below), asserting in part that "[f]or purposes of examination, the claims have been construed as encompassing nucleic acid fragments that manifest as "discrete bands of substantially equal intensity...when the fragments are resolved on a gel and stained" (specification at page 6, first full paragraph)" (Office action. Page 6, section 20). Applicant also notes that in sections 10-14 of the Office action (discussed above), the Examiner asserts that the claims are inoperative and therefore lack utility under 35 USC §101, yet in sections 15-38 the very same claims are asserted to be obvious over the Carlson and Stratagene references. By its very nature, an allegedly inoperative invention cannot be held obvious over an operative disclosure. Conversely, if the claims are held to be allegedly be obvious over prior disclosure, then they must necessarily be operative and have utility. Without taking a position as to whether the instant claims are ***either*** inoperative ***or*** obvious, Applicant respectfully submits that they cannot be both inoperative ***and*** obvious. Accordingly, Applicant requests that either the rejections under 35 USC §101 ***or*** 35 USC §103 be immediately withdrawn, ***or***

alternatively that the Examiner provide a rational explanation and underpinning as to how the very same claims can in one instance be "inoperative and lack utility", but in another instance be "obvious" over previously disclosed inventions.

V. Rejections Under 35 U.S.C. § 103:

Claims 141, 150, 155-157, 159-160 and 162-164 stand rejected under 35 USC §103(a) as allegedly being obvious over U.S. patent no. 5,316,908 to Carlson, *et al.* (hereinafter "Carlson") or Stratagene 1993 or Stratagene Catalog 1993. The Examiner states "[f]or purposes of examination, the claims have been construed as encompassing nucleic acid fragments that manifest as 'discrete bands of substantially equal intensity...when the fragments are resolved on a gel and stained' (specification at page 6, first full paragraph)" (Office action. Page 6, section 20) and asserts that Fig. 1 of Carlson discloses "multiple nucleic acid fragments that have the same intensity" (see Office action, page 6, section 21). Applicant respectfully disagrees with these rejections and submits that the interpretation of Carlson's Fig. 1 is incorrect for at least the following reasons. First, Fig. 1 of Carlson is not an accurate representation of the DNA markers that are disclosed. Instead, Fig. 1 is a "schematic, scale drawing of how the first and second molecular markers would migrate on an electrophoresis gel" (Carlson, Col. 2, lines 21-23; Emphasis added). A schematic drawing, by its very definition, represents elements of a system (e.g., band of a molecular weight ladder) using abstract, graphic symbols rather than realistic pictures. A schematic usually omits all details that are not relevant to the information the schematic is intended to convey, and may even add unrealistic elements that aid comprehension. Carlson's Fig. 1 is a drawing and the information represented in the drawing is prophetic. The drawing is meant to convey information relating to electrophoretic *migration* of the individual bands through a gel. There is nothing in Fig. 1 or in any of Carlson's disclosure that relates to or conveys any information about the *mass* of DNA in individual bands, as defined in the instant claims. The Examiner seems to make this same admission on page 7 of the Office action, noting "Fig. 1 is a drawing and not a photograph, the specification does state that the Figure does represent the *migration* of the nucleic acid ladder in an electrophoretic environment. Said Figure clearly shows that the bands have the same relative intensity" (Office action, page 7, section 23; Emphasis added). Therefore, by the Examiner's *own admission*, Carlson's Fig. 1 is merely a schematic representation of the migration of DNA bands, and is not an accurate representation of what the ladders actually look like during an electrophoresis experiment. Applicant respectfully submits that it is improper to extrapolate information relating to the **mass** of individual bands using Fig.1, since the intent

thereof was to represent band migration (i.e., band size), not mass (i.e., DNA content). Moreover, the very nature by which Carlson's DNA markers are made (i.e., by restriction digestion of a single larger λ-page DNA) is not conducive to the Examiner's interpretation of Fig. 1. In this regard Carlson clearly states "[t]he ladder is made up of pooled DNA restriction endonuclease digests" (Abstract). Carlson further states "[t]o make a restriction digest, .lambda. DNA was digested with one or two restriction endonucleases. The enzymes used for individual digests are indicated in Tables 2 and 3. Digestions were performed under standard conditions, generally according to the instructions of the enzyme's manufacturer. Restriction digests were pooled after digestion" (Carlson, Col. 4, lines 58 – 64). Therefore, if each band depicted in Fig. 1 were of equal intensity, as the Examiner claims, then the copy number of each of the bands would have to have been adjusted to compensate for the decrease in DNA mass of each band, since the bands in a single digest are present in an equimolar ration (i.e., assuming complete digestion of the λ-page DNA, mole equivalent of each of the resulting bands is 1:1…:1). There is no indication or suggestion in Carlson that the copy number of each band was adjusted so that the bands would show up on an electrophoresis gel with equal intensity. In fact, in Example 2 (First Marker Kit), Carlson explicitly states "[i]n the first ladder, the target DNA consisted of pooled *equal* amounts of 31 different restriction digests of phage λ DNA" (Carlson, Col. 4, last sentence; Emphasis added). If the input λ DNA of each digest was equal, as Carlson states, then each band should be visualized with its appropriate mass intensity, which was not adjusted. Yet, the intensity of each band constituting the molecular weight marker on the left side of Fig. 1 is equal, reinforcing Applicant's point that Fig. 1 is not a realistic representation of Carlson's marker set. In fact, the only indication that Carlson adjusted the amount of any of the individual bands in the marker set is found in Example 3: Second Marker Kit, which states in part "[t]he third improvement was to increase the amounts, i.e. relative copy number or the dosage, of the target DNA for the largest and smallest bands. Large DNA fragments blot inefficiently. As is well known in the art, small fragments are retained on membranes poorly during hybridization. Therefore, the signal from large DNA fragments and small DNA fragments tends to be less than the signal from bands in the middle range. This improvement compensated for that effect" (Carlson, Col. 5, lines 55-60). Table 3 (Carlson, Col. 7) outlines the size of each DNA fragment appearing on the right hand side of Fig. 1, along with its dosage compensation (either 3 or 1). According to Table 3, the smallest 526 bp fragment and the largest 22.6 kb fragment are present in equimolar amounts (i.e., 3-fold), which means that the 22.6 kb band contains 43-fold as on a DNA on mass basis as the 526 bp band, yet both bands are represented with equal intensity in Fig. 1. Additionally, if the 6.4 kb Ava II band is compared with the 5.8 kb Hae II band, both of which are similar to each other in size and which are depicted in Fig.

1 as bands with equal intensity, we see that the 6.4 kB Ava II band actually has 3.3-fold the amount (i.e., mass) DNA present in the 5.8 kb Hae II band (i.e., compare the 3 fold dose of the 6.4 kb band with the 1-fold dose of the 5.8 kb band). Despite this large differential in the actual amount of DNA present in each band, Carlson depicts the bands as having equal intensity in Fig. 1. Similarly, the 910 bp Eco RV/Bam HI band is compared with the 784 bp Dde I band, both of which are similar in size and which are depicted in Fig. 1 as bands with equal intensity, we see that the smaller 784 bp Dde I band actually has 2.6-fold the amount (i.e., mass) of DNA as the larger 910 bp Eco RV/Bam HI band (i.e., compare the 3 fold dose of the Dde I band with the 1-fold dose of the Eco RV/Bam HI band). The above serves to illustrate the fact that there is no correlation between the size, mass or relative mass and the depicted band intensity of the fragments shown in Carlson's Fig. 1, and no conclusion about same can be made.

In light of the arguments presented above, and by the Examiner's own statements, Applicant respectfully submits that Carlson fails to establish a *prima facie* case of obviousness against the instant claims. Neither of the two Stratagene references remedies this deficiency since they fail to address the incorrect interpretation of Carlson's schematic depiction of the bands. Accordingly, Applicant submits that claims 141, 150, 155-157, 159, 160 and 162-164 are unobvious and patentable over the Carlson and Stratagene references, taken alone or in combination and respectfully requests the rejections under 35 USC 103(a) be withdrawn.

CONCLUSION

The extendable due date for filing an Appeal Brief/Response to the most recent Office Action, under a two-month shortened statutory period, is **January 23, 2010**. Applicants therefore hereby petition for a **four (4)-month extension** of time under 37 C.F.R. § 1.136(a), thereby extending the due date for response to **May 23, 2010**. In association therewith, Applicants hereby authorize the Commissioner to charge Deposit Account No. 50-3994 in the amount of **$1,730.00**, the fee set forth under 37 C.F.R. § 1.17(a)(4). Applicants do not believe that any additional fees are due in connection with the filing of this paper. However, in the unlikely event that any such fees are due, the Commissioner is hereby authorized to charge the same to Deposit Account No. 50-3994, with reference to our matter IVGN 187.1 CON.

Respectfully submitted,

/Jonathan P. Aumais/
Jonathan P. Aumais, Ph.D.
Reg. No. 65,710
AGENT FOR APPLICANT(S)

LIFE TECHNOLOGIES CORPORATION
Intellectual Property Department
5981 Van Allen Way
Carlsbad, CA 92008
Phone: (760) 476-6271

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